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10/759,496	01/16/2004	Stefan Franzen	297/178/2	7690

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JENKINS, WILSON, TAYLOR & HUNT, P. A.
3100 TOWER BLVD
SUITE 1200
DURHAM, NC 27707

EXAMINER	
SISSON, BRADLEY L	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,496	FRANZEN ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43* is/are rejected.

7)☒ Claim(s) *28 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. Claims 28 and 29 objected to because of the following informalities: It does not appear that the claims end with a period (“.”). Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

4. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the

> invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co.; Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

The quantity of experimentation necessary

The quantity of experimentation necessary to practice the full scope of the invention is great- on the order of several man-years, with little if any reasonable expectation of success.

The amount of direction or guidance presented,

The specification provides general guidance as to how assays can be conducted. Such general statements, however, fail to disclose specific starting materials and reaction conditions that would enable the full scope of the invention. As noted below, the specification does comprise 5 examples, however, not all forms of nucleic acids are detected, and the specification fails to teach specific reaction conditions under which the full scope of the invention can be practiced. While hybridization has been studied for several years, the aspect of being able to accurately and reproducibly determine the change in temperature of nucleic acids on any solid surface (claim 1), is not known. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

The specification does not set forth reaction conditions and starting materials where any metal oxide is used, or where any solid support is used, or how any ligand-binding pair can be used in combination with the claimed method.

In accordance with claim 1, there is to be provided "a capture probe" and this probe is to hybridize to the target nucleic acid. Such language seemingly indicated that the probe is a nucleic acid of some sort. However, claim 14 stipulates that "the detection probe further comprises an oligonucleotide." If the oligonucleotide is added in claim 14, there can be no oligonucleotide probe in claim 1. Accordingly, it is not clear how hybridization is taking place without the presence of a nuclei acid/oligonucleotide.

In accordance with claim 16, the probe comprises a nanoparticle, and that it further comprises one member of a binding pair, and that the target sequence comprises the other member of the binding pair. If he binding between the probe and the target are through the binding pair, then it does not seem possible that there is any hybridization taking place in claim1, as is required. The specification is silent as to how this is achieved.

The presence or absence of working examples

The specification provides 5 working examples.

Example 1, "X-Ray Photoelectron Spectroscopy Characterization of ITO Electrode Surfaces Modified By Single Stranded DNA And Gold Nanoparticles," pp. 57-59;

Example 2, "Infrared Reflection Absorption Spectroscopy (IRRAS)," p. 59;

Example 3, "LITJ At Gold Nanoparticle-Coated ITO Electrodes," pp. 60;

Example 4, "Infrared Thermography of Gold nanoparticles," pp. 61-62; and

Example 5, "DNA Detection With infrared Thermography," page 62.

The nature of the invention

The claimed invention relates directly to matters of chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The state of the prior art and the predictability or unpredictability of the art

Prior, as well as post-filing art teaches of numerous problems confronting those of ordinary skill in the art. These problems have not been addressed by the instant disclosure. Absent specific guidance as to how these issues are to be overcome, one of ordinary skill in the art would be forced to trial-and-error experimentation in an effort to overcome these known issues.

Zhang et al., *Bioinformatics*, Vol. 19, No. 1, 2003, page 14, states:

> It is widely recognized that the hybridization process is prone to errors and that the future of DNA sequencing by hybridization is predicated on the ability to successfully cope with such errors. However, the occurrence of hybridization errors results in the computational difficulty of the reconstruction of DNA sequencing by hybridization. The reconstruction problem of DNA sequencing by hybridization with errors is a strongly NP-hard problem. So far the problem has not been solved well.

Chan (US Patent Application Publication US 2002/0119455 A1):

> [0018] In practice, Probe Up methods have been used to generate sequences of about 100 base pairs. Imperfect hybridization has led to difficulties in generating adequate sequence. Error in hybridization is amplified many times. A 1% error rate reduces the maximum length that can be sequenced by at least 10%. Thus if 1% of 65,536 oligonucleotides gave false positive hybridization signals when hybridizing to a 200-mer DNA target, 75% of the scored "hybridizations" would be false (Bains, 1997). Sequence determination would be impossible in such an instance. The conclusion is that hybridization must be extremely effective in order to generate reasonable data. Furthermore, sequencing by hybridization also encounters problems when there are repeats in sequences that are one base less than the length of the probe. When such sequences are present, multiple possible sequences are compatible with the hybridization data. (Emphasis added.)

As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

- The purity of the nucleic acid preparation.

- Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.
- Length of homologous base sequences- any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.
- Ionic strength- the rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.
- Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.
- Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.
- Denaturing reagents- the presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.
- Incubation- the longer the incubation time, the more complete will be the hybridization.
- Volume exclusion agents- the presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

- Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

Barany et al. (US 2007/0042419 A1), at paragraph 0036 teaches in part:

> For allele-specific oligonucleotide hybridization ("ASO"), the mutation must be known, hybridization and washing conditions must be known, cross-reactivity is difficult to prevent, closely-clustered sites due to interference of overlapping primers cannot undergo multiplex detection, and mutant DNA cannot be detected in less than 5% of background of normal DNA.

Choi et al. (US 2007/0042400 A1), at paragraph 0035, teach:

> [0035] In conventional methods of preparing nucleic acid, polysaccharides such as starch often co-precipitate with nucleic acid. When polysaccharides co-precipitate with nucleic acid, it is difficult to manipulate nucleic acids by amplification methods, such as PCR, or by other detection methods, such as hybridization detection. Polysaccharides may also inhibit digestion with restriction endonucleases and other enzymatic manipulations.

It is noted that the claimed method fairly encompasses the use of genomic DNA, and the use of an enzyme substrate as a label.

Yasuno et al., (US 2007/0031829 A1), paragraph 0037, teach in part:

> Certain oligonucleotides hybridize to polynucleotides having complementary sequences. Although DNA hybridization is sequence-specific, it is difficult to completely exclude hybridizations towards very similar nucleotide sequences.

Wang et al., (US 2007/0009954 A1), teach:

> [0004] A number of methods have been developed to score SNPs, including allele-specific hybridization, electrophoretic DNA sequencing, single-nucleotide extension using labeled chain terminators, the "Invader" assay (Third Wave Technologies, Madison Wis.), mass spectrometry, the 5' nuclease assay (Taqman; see below), etc. All of these

> methods entail assays that are either difficult or expensive to develop, or difficult or expensive to perform.

Rowlen et al., (US 2006/0286570 A1) teach:

> [0004] A variety of methods exist for detection of molecular recognition events. Detection of molecular recognition events such as DNA hybridization, antibody-antigen interactions, and protein-protein interactions becomes increasingly difficult as the number of recognition events to be detected decreases.

It is noted that the claimed method places no lower limit on the ability to accurately and reproducibly detect any binding between polymer and unit specific markers.

As evidenced above, the art is replete with known issues that directly impact the enablement of the claimed invention. A review of the instant disclosure fails to identify how these art-recognized issues are to be overcome such that the full scope of the invention can be practiced without the public having to resort to undue experimentation.

The breadth of the claims

The claims fairly encompass the detection, and ultimately sequencing, of any nucleic acid as a result of the formation of hybridization products. The target nucleic acid is not required to be free of other materials, including but not limited to partially complementary sequences found in the sample. Further, the method fairly encompasses nucleic acids, be it target and/or probe, that can form secondary structures with self, e.g., hairpin loops. In such a situation, the probe as well as the target would generate a thermal image of hybridization having taken place. The problem when the probe does such is that a false positive signal is obtained. When the nucleic acid in the

sample does it, and the sample nucleic acids does not comprise the desired target sequence, one would also obtain a false positive signal as well.

The claimed method encompasses the use of any hybridization conditions, any surface, nanoparticles of any size, shape and composition, and the use of any wavelength of light that could be absorbed by the nanoparticle.

5. In view of the breadth of scope clamed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled by the disclosure. Therefore, and in the absence of convincing evidence to the contrary, claims 1-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Response to argument

6. At page 10, bridging to page 13 of the response received 22 December 2006, argument is presented as to what one of skill in the art would have been able to do or would have concluded after reading he instant disclosure. This argument has been fully considered and has not been found persuasive. Attention is directed to MPEP 2145.

> Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.
> The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

For the above reasons, and in the absence of convincing evidence to the contrary, claims 1-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 1-43 are rejected as to just what constitutes the metes and bounds of "nanoparticle."

10. At page 8 of the response received 22 December 2006, argument is made that the term is art-recognized and that one of skill in the art would know what it means. This argument has been fully considered and has not been found persuasive. Attention is directed to MPEP 2145; *supra*.

11. It is further noted that while the term does find use in the art, there is no one set definition for it. In support of this position, attention is directed to the following documents.

12. Take (US Patent Application Publication US 2006/0094860 A1) disclose "nanoparticles" that take of not only spherical shapes but that of a bar, and which range in size from 2 nm to 200 nm.

13. Chow et al., (US Patent Application No. 2006/0099146 A1) disclose nanoparticles that range in size from 1 to 1000 nm, and which can have "any size, shape or morphology."

14. Fisher et al., (US Patent Application Publication 2006/0099148 A1), disclose at paragraph 0012 that the nanoparticles range from 5 nm to 50 nm.

15. Clearly, the range from upper limits of 50 nm to 1000 nm (20 orders of magnitude), and where the particle may be spherical or "approximately spherical" (applicant's) as well as in any shape and have any morphology, do not suggest that the term "nanoparticle" has a singular definition. Given such a showing, and in the absence of convincing evidence to the contrary, one would not necessarily know the metes and bounds of the claims. Therefore, and in the absence of convincing evidence to the contrary, claims 1-43 are rejected under 35 USC 112, second paragraph.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

17. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

19. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

20. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS